Remarks

Claims 21-25, 28, and 33-41 are pending in the present application. The following rejections are at issue and are set forth by number in the order in which they are addressed:

1. Claim 32 is objected to under 37 CFR 1.75 as being a duplicate of Claim 26;
2. Claims 21 and 31 are rejected under 35 U.S.C. §102(e) as being anticipated by Dirks et al. (U.S. Pat. No. 6,060,273);
3. Claims 21-24, 26, and 31-32 are rejected under 35 U.S.C. §102(e) as being anticipated by Piechaczyk et al. (Appl. No. 2002/0168339);
4. Claims 21-25 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Dirks et al. (U.S. Pat. No. 6,060,273) in view of Voet and Voet, Biochemistry (1990) pp 1099-1100;
5. Claims 21, 22-28, and 31-33 are rejected under 35 U.S.C. §112, second paragraph, as indefinite; and
6. Claims 21-28 and 31-33 are rejected under 35 U.S.C. §112, first paragraph, as lacking an adequate written description.

Claim 21 has been amended in order to further define one embodiment of the present invention and to further their business interests and the prosecution of the present application in a manner consistent with the PTO's Patent Business Goals (PBG; 65 Fed. Reg. 54603 (September 8, 2000), and not in acquiescence to the Examiner's arguments and while reserving the right to prosecute the original (or similar) claims in the future. The amendment to claim 21 finds more than ample support in the specification and the claims as originally filed. Applicants have canceled, without prejudice, claims 27 and 32 for similar reasons. None of the claim amendments made herein are related to the statutory requirements of patentability. None of the claim amendments made herein are intended to narrow the scope of any of the amended claims within the meaning of *Festo Corp. v. Shokestu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir. 2000) or related cases.

New claims 34-41 have been added. Support for these claims can be found in the claims as originally filed, the summary of the invention, and pages 31-33 and 48-49 of the specification,

among other places.

1. The double patenting rejection is moot

Claim 32 is objected to under 37 CFR 1.75 as being a duplicate of Claim 26. Claim 32 has been canceled, thus this rejection is moot. This claim has been deleted in order to further define one embodiment of the present invention and to further applicant's business interests and the prosecution of the present application in a manner consistent with the PTO's Patent Business Goals (PBG), and not in acquiescence to the Examiner's arguments and while reserving the right to prosecute the original (or similar) claims in the future. Thus, this claim cancellation is not related to the statutory requirements of patentability and is not intended to narrow the scope of any of the amended claims within the meaning of *Festo* or related cases.

2. Claims 21 and 31 are not anticipated

Claims 21 and 31 are rejected under 35 U.S.C. §102(e) as being anticipated by Dirks et al. (U.S. Pat. No. 6,060,273). The Federal Circuit has stated the relevant analysis for anticipation as follows:

> A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."

Verdegaal Bros. V. Union Oil Co. Of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claim 31 is canceled so the rejection as to that claim is moot. Applicants respectfully submit that Claims 21 and 31 are not anticipated by Dirks et al. because Dirks does not teach the use of retroviral vectors as required by Claim 21. Likewise, the newly added claims (Claims 34-41) are not anticipated because Dirks et al. does not teach a vector comprising a signal peptide sequence operably linked to an internal ribosome entry site, wherein the second codon of said signal peptide sequence is GCC. Thus, applicants respectfully submit that this ground of rejection has been rebutted and request that the claims be passed to allowance.

3. Claims 21-24, 26, and 31-32 are not anticipated

Claims 21-24, 26, and 31-32 are rejected under 35 U.S.C. §102(e) as being anticipated by Piechaczyk et al. (Appl. No. 2002/0168339). The Examiner states that "Absent evidence to the contrary, the subunits are expressed at about a 0.9:1.1 ratio as equimolar ratios of the heavy and light chains are required for immunoglobulin assembly . . . ." (Office Action, p. 3-4).

Applicants respectfully submit that the Examiner's legal and scientific reasoning is unsound. It appears that in making this rejection, the Examiner is relying on an anticipation by inherency as the Examiner has pointed to no specific teaching of a .09-1.1 to 1:1 ratio in Piechaczyk, nor could Applicants find any such teaching.

The Federal Circuit has established the relevant evidentiary standards for proving anticipation by inherency:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

Continental Can Company USA, Inc., v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991) (emphasis added) (holding no anticipation due to inherency). Thus, argued gaps in a reference must be filled by evidence that clearly shows the descriptive matter is **necessarily present**. This is a far more stringent standard than the standard urged by the Examiner. Indeed, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269 (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981).

In the present case, the Examiner is relying on possibilities. Indeed, in place of the correct standard, the Examiner uses an inappropriate "absent evidence to the contrary standard". The Examiner has cited no extrinsic evidence establishing that the missing claim element is necessarily present in the thing described in the reference. As held by the Federal Circuit, the Examiner cannot rely on the reasoning that a certain thing may result from a given set of circumstances. The Examiner must do something to "fill in the gap."

Moreover, Applicants respectfully submit that the instant application establishes that the Examiner's scientific reasoning is incorrect. The Applicants noted a problem in the art that gene

following the IRES sequence is often expressed at much lower levels than the gene preceding the IRES sequence. At pages 31-33 of the specification the Applicants describe the development of methods for solving this problem and ensuring that the gene following an IRES sequence is expressed at the same level as the gene preceding the IRES. These methods involve modification of the signal peptide sequence of the gene following the IRES.

The inventors of the instant application contemplate that equimolar expression of heavy and light chains leads to the formation of more functional immunoglobulin molecules per cell. However, equimolar expression is not necessary for the production of functional immunoglobulins. Indeed, functional immunoglobulins are often expressed from cells that do not demonstrate equimolar expression of heavy and light chains. In such cells, a large number of incorrectly assembled immunoglobulin molecules are often formed along with the functional immunoglobulins. Thus, the Applicants respectfully submit that the Examiners reasoning is flawed and that Piechaczyk does not teach element of the claims. Expression of **some** functional immunoglobulins is not indicative of expression of immunoglobulin chains in an equimolar ratio.

Likewise, Applicants respectfully note that Piechaczyk does not teach a vector comprising a signal peptide sequence operably linked to an internal ribosome entry site, wherein the second codon of said signal peptide sequence is GCC. Therefore, Piechaczyk does not anticipate new Claims 34-41.

Applicants respectfully submit that this ground of rejection has been rebutted and request that the claims be passed to allowance.

4. The claims are not obvious

Claims 21-25 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentbale over Dirks et al. (U.S. Pat. No. 6,060,273) in view of Voet and Voet, Biochemistry (1990) pp 1099-1100. A *prima facie* case of obviousness requires the Examiner to provide a reference(s) which (a) discloses all of the elements of the claimed invention, (b) suggests or motivates one skilled in the art to combine the claimed elements to produce the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements precludes a finding of a *prima facie* case of obviousness and without more entitles the Applicants to allowance of the claims in issue. *See,*

e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990). In addressing this rejection, Applicants focus on the independent claims since the non-obviousness of independent claims necessarily leads to the non-obviousness of claims dependent thereon.[1]

The cited references fail to teach each element of the claims at issue. In particular, neither Dirks nor Voet and Voet teach the use of retroviral vectors. Thus, a *prima facie* case of obviousness is not established for Claims 21-25. Furthermore, neither Dirks nor Voet and Voet teach a vector comprising a signal peptide sequence operably linked to an internal ribosome entry site, wherein the second codon of said signal peptide sequence is GCC. Thus, new Claims 34-41 are free of the prior art as well.

Accordingly, the Examiner has not established a *prima facie* of obviousness with respect to the claims at issue. Applicants respectfully request that the claims be passed to allowance.

5. The claims are definite

Claims 21, 22-28, and 31-33 are rejected under 35 U.S.C. §112, second paragraph, as indefinite. Applicants respectfully submit that this rejection rendered moot by replacing the term "antibody" with the term "immunoglobulin" in Claim 21. This claim has been amended in order to further define one embodiment of the present invention and to further applicant's business interests and the prosecution of the present application in a manner consistent with the PTO's Patent Business Goals (PBG), and not in acquiescence to the Examiner's arguments and while reserving the right to prosecute the original (or similar) claims in the future. Thus, this claim cancellation is not related to the statutory requirements of patentability and is not intended to narrow the scope of any of the amended claims within the meaning of *Festo* or related cases.

6. The claims are supported by an adequate written description

Claims 21-28 and 31-33 are rejected under 35 U.S.C. §112, first paragraph, as lacking an adequate written description. In particular, the Examiner states that the claims contain "subject matter which was not described in the specification in such a way as to reasonably convey to one

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1 §MPEP 2143.03.

skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." (Office Action, p. 6). The Examiner admits that "applicants teach the production of MN14, LL2, and botulinum toxin immunoglobulin heavy and light chains." (Office Action, p. 7). The Examiner goes on to state that:

> The genomic version of any of the recited genes is not disclosed by the specification nor does the prior art apparently disclose the entire gene. While the cDNAs may be known, not all of the genes have been characterized. Because all of the components of the gene such as regulation sequences, introns, and exons must be determined empirically in order to generate the immunoglobulin genes, applicant claims the gene without any disclosure about its structure. The skilled artisan would not conclude that the applicant was in possession of a viral vector comprising the claimed genes. (Office Action, p. 7).

Applicants respectfully disagree for the following reasons. At the outset, it appears that the standard for written description utilized by the Examiner is derived from the Written Description Guidelines issued by the U.S.P.T.O. However, the position taken by the Examiner in the instant case is contrary to those guidelines.

Example 18 of the Written Description Guidelines is directed to a process claim where the novelty is in the method steps. This example is analogous to the instant claims where the novelty is in a method for producing immunoglobulin heavy and light chains in a ratio of 0.9-1.1 to 1:1. The analysis section of Example 18 notes that a particular nucleic acid is not essential to the claimed invention. Furthermore, there is actual reduction to practice of only a single embodiment. The Example concludes that the claimed invention is adequately described.

As in Example 18, particular immunoglobulin sequences are not essential to the claimed invention. In other words, the invention is not directed to the production of particular immunoglobulins, but to immunoglobulins in general. Thus, the disclosure of the expression of several (as opposed to one sequence in Example 18) different immunoglobulin sequences is more than adequate to prove that the Applicants were in possession of the methods necessary to practice the claimed invention. Applicants respectfully submit that following from Example 18 of the Written Description Guidelines, the Examiner's focus on immunoglobulin coding sequences is misplaced.

Applicants further direct the Examiner to the definition of gene appearing in the specification at page 7:

> The term "gene" refers to a nucleic acid (*e.g.*, DNA or RNA) sequence that comprises coding sequences necessary for the production of a polypeptide or precursor (*e.g.*, proinsulin). The polypeptide can be encoded by a full length coding sequence or by any

> portion of the coding sequence so long as the desired activity or functional properties (*e.g.*, enzymatic activity, ligand binding, signal transduction, etc.) of the full-length or fragment are retained. The term also encompasses the coding region of a structural gene and includes sequences located adjacent to the coding region on both the 5' and 3' ends for a distance of about 1 kb or more on either end such that the gene corresponds to the length of the full-length mRNA. The sequences that are located 5' of the coding region and which are present on the mRNA are referred to as 5' untranslated sequences. The sequences that are located 3' or downstream of the coding region and which are present on the mRNA are referred to as 3' untranslated sequences. The term "gene" encompasses both cDNA and genomic forms of a gene. A genomic form or clone of a gene contains the coding region interrupted with non-coding sequences termed "introns" or "intervening regions" or "intervening sequences." Introns are segments of a gene which are transcribed into nuclear RNA (hnRNA); introns may contain regulatory elements such as enhancers. Introns are removed or "spliced out" from the nuclear or primary transcript; introns therefore are absent in the messenger RNA (mRNA) transcript. The mRNA functions during translation to specify the sequence or order of amino acids in a nascent polypeptide.

Thus, the Applicant's stated definition of "gene" is a nucleic acid sequence "that comprises coding sequences necessary for the production of a polypeptide or precursor . . . ." Applicants respectfully note that the specification provides multiple examples of suitable coding sequences that can be used in the present invention. Applicant need not provide multiple, gratuitous examples of additional coding sequences (including genomic sequences) that are known in the art. Indeed, by the priority date of the present application, many examples of immunoglobulin coding sequences were available in public databases.

As the Federal Circuit has held, patent applications are addressed to those of skill in the art:

> Requiring inclusion in the patent of known scientific/technological information would add an imprecise and open ended criterion to the content of patent specifications, could greatly enlarge the content of patent specifications and unnecessarily increase the cost of preparing and prosecuting patent applications, and could tend to obfuscate rather than highlight the contribution to which the patent is directed. A patent is not a scientific treatise, but a document that presumes a readership skilled in the field of the invention.

Anijomoto v. Archer-Daniels-Midland, 228 F.3d 1338, 1346-47 (Fed. Cir. 2000) (finding that patent described the best mode sufficient to satisfy §112).

The inventors simply are not required to describe in detail what is known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (holding that "a patent need not teach, and preferably omits, what is well known in the art");

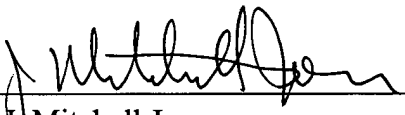
Patent Office Guidelines, 66 Fed. Reg. at 1106 ("What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail."). Apparently, the Examiner would have the Applicants include multiple examples of known sequences in their application. The inclusion of such known material is not required by the law, and indeed, should be omitted from the application.

Accordingly, Applicants respectfully submit that the rejection of the claims as lacking an adequate written description has been traversed and that the claims should be passed to allowance.

CONCLUSION

All grounds of rejection and objection of the Office Action of April 23, 2003 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: July 23, 2003



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